



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

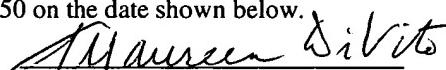
Applicant: Liu et al.) Examiner: R. Joynes
Serial No.: 09/970,020)
Filed: October 3, 2001) Art Unit: 1615
Entitled: **Developing A Delivery System**) Confirmation No.: 8697
 For Multi-Pharmaceutical Active)
 Materials at Various Release Rates) Atty. Docket No.: 107223-139 US

CERTIFICATION UNDER 37 C.F.R. § 1.10

I hereby certify that the attached papers are being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" Mailing Label No. EV207578213US addressed to: **Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450** on the date shown below.

April 14, 2004

Date of Signature and of Mailing


Maureen DiVito

REPLY BRIEF UNDER 37 C.F.R. § 1.193

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants submit this Reply Brief in response to the Examiner's Answer mailed on March 10, 2004. An original and two copies of this Brief are submitted herewith. The following remarks are responsive to the Examiner's Answer.

I. ARGUMENT

Appellants claim orally administrable pharmaceutical compositions that include an immediate release formulation of one enantiomer of a chiral compound, and a controlled release formulation of another enantiomer of a chiral compound. Controlled release is effected by a heteropolysaccharide and polysaccharide gum excipient. Appellants' claims 24-54 stand rejected under 35 U.S.C. § 103(a).

Appellants maintain that claims 24-54 are not obvious under 35 U.S.C. § 103(a) over the cited references, Gilbert et al., WO 98/40053 ("Gilbert") in combination with Baichwal et al.,

Appellants maintain that claims 24-54 are not obvious under 35 U.S.C. § 103(a) over the cited references, Gilbert et al., WO 98/40053 (“Gilbert”) in combination with Baichwal et al., U.S. Patent No. 4,994,276 (“Baichwal”). *Prima facie* obviousness has not been established, because there would have been no motivation to combine the cited references except based on improper hindsight in view of Appellants’ invention.

Prima facie obviousness requires that there be some motivation to combine the cited references that is not based on improper hindsight reconstruction in view of the claimed invention. In particular, the Examiner must identify reasons why one of ordinary skill in the art without knowledge of the claimed invention would have chosen the elements from the cited references for combination as claimed, and should “explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination.” *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998). The showing of motivation to combine must be clear and particular, based on actual evidence, and not merely broad conclusory statements regarding the teachings of multiple references. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citation omitted).

Gilbert teaches a two-part dosage form for releasing enantiomers of a chiral drug at different rates, and refers generally to the use of conventional controlled release technology in such dosage forms. *See, e.g.*, Abstract and page 6, lines 9-13, 19-20, and 30-35. Baichwal teaches a particular heteropolysaccharide and polysaccharide gum excipient for controlled release delivery of a drug. *See, e.g.*, column 4, lines 8-54. Nothing in Baichwal suggests use of the disclosed excipient in two-part formulations providing separate delivery rates for enantiomers of a chiral drug. Similarly, nothing in Gilbert suggests the use of a specific heteropolysaccharide and polysaccharide gum excipient for controlled release in the disclosed formulations. On the contrary, Gilbert exemplifies the use of a hydroxypropyl methyl cellulose (HPMC) controlled release excipient for its bi-layer tablets. The Examples of Gilbert indicate that the HPMC excipient provides a suitable controlled release profile for the bi-layer tablets, and that the controlled release profile can be adjusted as desired by altering the quantity of HPMC. *See Examples 2-3, page 9, line 15 – page 10, line 17.* Thus, there is no deficiency in the teachings of Gilbert that would motivate one of ordinary skill in the art to seek out an alternative to the disclosed HPMC controlled release excipient for making a two-part formulation.

Accordingly, without the benefit of Appellants' disclosure, there would have been no motivation for one of ordinary skill in the art to substitute Baichwal's heteropolysaccharide and polysaccharide gum excipient for the HPMC excipient described and enabled by Gilbert.

Despite continual assertions to the contrary, the Examiner still has not provided the requisite clear and particular showing of motivation to combine. The Examiner asserts that one would be motivated to use the excipient of Baichwal in the formulations of Gilbert because Baichwal's excipient is inexpensive, easily compressible, and compatible with many drugs. *See, e.g.,* Examiner's Answer, page 4, lines 9-15. However, such conclusory statements regarding the general advantages of Baichwal's excipient do not suffice in view of the vast number of available controlled release technologies, each of which may have their own particular advantages. The Examiner simply has not identified any specific reason except one based on improper hindsight in view of Appellants' invention why one of ordinary skill in the art would choose the excipient of Baichwal from among a wide array of useful options, including the readily acceptable HPMC excipient taught by Gilbert itself, to prepare a two-part formulation.

The Examiner argues that every obviousness rejection in some sense necessarily constitutes a hindsight-based reconstruction. Such reconstruction is asserted to be proper as long as the analysis considers only knowledge that was within the level of ordinary skill in the art at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure. *See, e.g.,* Examiner's Answer, page 7, lines 5-12. This argument does not save the present obviousness rejection, because the requisite motivation to combine must be gleaned from Appellants' disclosure. Information within the knowledge of one of ordinary skill in the art prior to Appellants' invention simply does not provide any motivation to select Baichwal's excipient from among thousands of useful controlled release delivery systems for employment in the formulations of Gilbert.

Unable to cure this fatal deficiency in the obviousness analysis, the Examiner has focused on criticizing the search results cited by Appellants to illustrate the large number of references in the PTO patent database alone that disclose controlled release delivery systems. For example, the Examiner asserts that “[t]he search of the Appellants does not show that the 2,000 references all teach controlled release systems. Many references exist within the U.S. databases that may mention controlled release systems but do not actually teach an invention that **IS** a controlled release system.” Examiner's Answer, page 6, lines 13-16. However, the independent

inventiveness of the various controlled release technologies disclosed in the search results is not relevant. The search results were cited simply as one exemplary indication of the huge volume of literature that has been published regarding countless different controlled release formulations. The Examiner's dissatisfaction with the chosen search terms does not rebut the fundamental premise that there are a very large number of known, useful controlled release technologies. Indeed, the Examiner has never asserted otherwise, and still has not identified a plausible reason why one of ordinary skill in the art would be motivated to select the particular excipient of Baichwal from an exceedingly broad range of available useful options.

In sum, given the vast number of conventional controlled release mechanisms, and given Gilbert's exemplification of HPMC in particular, there would be no motivation for one of ordinary skill in the art without knowledge of Appellants' invention to select the particular excipient of Baichwal for use in Gilbert's two-part formulations. This lack of motivation to combine is necessarily fatal to the obviousness rejection. See *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (claimed compound not obvious where cited reference teaches vast number of compounds and discloses typical or preferred compounds different from claimed compound, and thus does not suggest selection of claimed compound) (citing *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (claimed nucleic acid sequences not obvious over reference teaching almost infinite possibilities and not suggesting why one would choose the claimed sequences)); *In re Herschler*, 591 F.2d 693, 702 (C.C.P.A. 1979) (claimed combination of steroid and solvent DMSO not obvious where references teach general utility of DMSO as a solvent but there is no suggestion to choose DMSO from among countless numbers of solvents).

The U.S. Court of Appeals for the Federal Circuit has warned that it is improper to "use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Moreover, "the best defense against hindsight-based obviousness analysis is rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references." *Ecolochem, Inc. v. Southern California Edison Co.*, 277 F.3d 1361, 1371 (Fed. Cir. 2000) (citation omitted). Contrary to these legal principles, the Examiner has improperly used Appellants' disclosure as a guide to cherry pick the teachings of Gilbert and Baichwal from among thousands of references teaching useful pharmaceutical formulations and controlled release excipients. Without the benefit of Appellants' disclosure, one of ordinary skill in the art

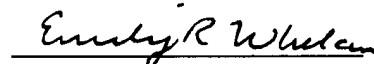
simply would not have been motivated to select these two particular references for combination. Accordingly, Appellants respectfully submit that the rejection of claims 24-54 under 35 U.S.C. § 103(a) is based on improper hindsight reconstruction, and should be reversed.

II. CONCLUSION

For the reasons advanced above, Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejection, remand the application to the Examiner, and direct the Examiner to issue a Notice of Allowance.

No fees are believed to be due in connection with the filing of this Reply Brief. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

Respectfully Submitted,


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Dated: 4/14/04

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